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AKERMAN SENTERFITT
P.O. BOX 3188
WEST PALM BEACH, FL 33402-3188

EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,729	ROLDAN ET AL.	
	Examiner	Art Unit	
	ROY P. ISSAC	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33,35-37,40-45 and 47-65* is/are pending in the application.

4a) Of the above claim(s) *47-53 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-33, 35-37, 40-45, 47-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/830,734 (July 27, 2001), now U.S. Patent 6,605,603, which is a 371 of PCT/EP99/08269 (October 29, 1999) which claims priority to Argentina P 98 01 05446 (October 30, 1998).

This Office Action is in response to Applicant's amendment/ remarks/ response filed 1/2/08, wherein claim 39 was cancelled, claim 62 was amended, and claims 63-65 were newly submitted. Applicants' submission of exhibits A-D is acknowledged.

Rejections Withdrawn

In view of the cancellation of claim 39, all rejections made with respect to claim 39 in the previous office action are withdrawn.

Applicants' amendments deleting the terms "osteoporosis", "arthritis" and "peridental osteopenia" overcomes the rejection of claim 62 under section 102(b) over van Beek et.al.

Applicant's arguments, see page 13-14, filed 1/2/08, with respect to the rejection of claims 32-33, 35-37, 40-45, 54 and 58-62 under section 112, first paragraph as lacking written description have been fully considered and are persuasive. The rejection of claims 32-33, 35-37, 40-45, 54 and 58-62 has been withdrawn.

Applicants' arguments directed to the rejection of claims 42 under section 112, second paragraph, see page 16 last two paragraphs, was found persuasive. The rejection of claim 42 under section 112, second paragraph is withdrawn.

The following are new or modified rejections necessitated by Applicant's amendment filed 1/2/08, wherein claim 29 was cancelled, and claim 62 was amended and claims 63-65 were newly submitted. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, mailed 10/02/07, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-33, 35-37 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to the method for maintaining a healthy bone structure by administration of a bisphosphonic compound to a patient without an osteopathy. The instant specification fails to provide information that would allow

the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The invention herein is related to a method of maintaining a healthy bone structure comprising administering to a patient without an osteopathy a medicament comprising NH2-OPD. Note that, "maintaining a healthy bone structure" in a "patient without an osteopathy" would require the patient not to develop any osteopathies. This is considered a preventive method.

The state of the prior art:

The prior art includes the use of NH2-OPD for the treatment of a variety of diseases including urolithiasis (kidney stones etc.), ectopic calcifications, osteoporosis, arthritis and periodontal diseases. (WO 97/02827; Of Record). The prior art does not show the administration of NH2-OPD to a patient without an osteopathy. Osteopathy is considered any type of bone disease or disorder of

any condition effecting bones. The prior art does not show how to identify a patient without any bone disease, disorder or any condition effecting bones. For example, osteoporosis is often diagnosed in patients by scanning bone mineral densitimometry methodologies and developing T-Score for risk population. (Miller PD, Rev. Endocr. Metab. Disord. 2006, 7, 75-89; Of record). The T-Score sets an intervention threshold for treatment of osteoporosis. However, many patients would develop fractures even though they are not in the osteoporosis risk profile. (Pages 75-56). Miller discusses the various parameters in determining T-Score and its utility in predicting osteoporosis. The fracture risk varies for different parts of the body as well as between patient population, ethnicity, race and gender.

The claims herein are directed to treatment of a "patient without an osteopathy". This recitation is interpreted as a patient without any osteopathies. The existing methodology cannot identify with certainty patients that are at risk for osteoporosis. Osteopathy is a much broader term than osteoporosis, and includes any type of bone disorders, diseases and conditions effecting bones. It is highly unlikely that the administration of NH2-OPD can maintain the bone structure without any types of osteopathies from developing. One of skill in the art would consider it likely that the administration of NH2-OPD to a patient without any osteopathies would result in the formation of bone spurs, calcifications etc. Concentration of mineral in bone is partially controlled by the activities of tow classes of cell: osteoclast cells and osteoblast cells. Osteoblast cells function in the formation of bone while osteoclast cells function in the

destruction or "resorption" of bone. As applicants admits, (See Paragraph 2, Page 21, response filed 7/20/2007) that, in healthy persons there is a balance between the activity of osteoclast and osteoblast cells that maintain a sufficient level of bone strength while preventing the formation of unhealthy "overgrown" bone structures. One of skill in the art would view the administration of NH2-OPD to healthy patients to change the balance between osteobalst/ osteoclast activity and thus, resulting in a variance from the maintenance of the osteopathy-free condition.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.S. or equivalent advanced degree.

The predictability or lack thereof in the art: the instant claimed invention is highly *unpredictable* as discussed below:

Maintaining healthy bone structure is not the same as the treatment of a disease condition associated with bone structure. In order to maintain healthy bone structure by preventing a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease, which would be required to maintain a healthy bone structure. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer. Thus, it is highly unlikely that any of the administration of healthy bone structure can be achieved by the administration of the compositions of the instant application.

The presence or absence of working examples:

The specification does not provide any examples of the administration of NH2-OPD to any patients. The specification does not provide any guidance for identifying a patient without any osteopathy. No examples of administration of NH2-OPD to a patient without an osteopathy is disclosed. There are no

examples of maintenance of bone structure by a subject without any osteopathy due to the administration of NH2-OPD.

The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

The quantity of experimentation necessary:

There are no clear cut limitations on when a patient has an osteopathy versus when they don't. Many of the bone related diseases are progressive diseases, and most can only be diagnosed after they have multiple symptoms. Thus, how would a skilled artisan know when a patient has an osteopathy, versus when they are without an osteopathy? How is it determined? It is not clear which ones do applicant point to as representative of "a patient without an osteopathy"? Does a patient without an osteopathy have NO clinical signs? OR, do they have some clinical signs, but are still considered "healthy" (i.e. no outward appearance of osteopathy).

In order to determine whether the claimed method can maintain a healthy bone structure, one of ordinary skill in the art will need to answer the questions posed above, which will require significant intellectual and financial input, and an effort that will be collaborative in nature with clinical physicians, organic chemists and biochemists involved, resulting in enormous burden on one of skill in the art to practice the invention as claimed.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the maintenance of healthy bone structure by administration to a patient without an osteopathy NH2-OPD.

Genentech, 108 F.3d at 1366, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the ***Wands*** factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants argue that the claims do not include limitation that the patient fails to develop any osteopathy. However, maintaining a condition of bone structure wherein the patient is "without an osteopathy" requires that the patient does not develop any osteopathy. Applicants further argue that a step of diagnosing an osteopathy is not relevant to instant application since diagnosis is not claimed. However, it is not clear how the instant claims can be practiced without determining who is "a patient without an osteopathy". Applicants submission of exhibits were fully considered and found unpersuasive since they are directed to detecting osteoporosis rather than ruling out all osteopathies to

identify "a patient without an osteopathy". Identifying a patient as one without osteoporosis does not mean that patient is "without an osteopathy". It just rules out one of the many conditions that can be considered an osteopathy. Applicant seems to interchangeably use the terms osteoporosis and osteopathy, not clearly delineating the scope of these two terms. Applicant further states that the office action sets out a definition of "maintaining a healthy bone structure" that the applicant disagrees with. However, the office action does not define the phrase as such. The office action considers relevant issues related to "maintaining a healthy bone structure" wherein the patient is "without an osteopathy". The claims herein are not directed to maintaining just any bone structure, but a bone structure "without an osteopathy". Applicant takes the comments out of context when the focus is on maintaining a healthy bone structure, but without considering that such bone structure must be without any osteopathies. Applicant admits that which patient may or may not develop an osteopathy is subject to some level of uncertainty. (see page 13, second paragraph). Applicants further argue that "as with any prophylactic measure, it can be anticipated with confidence that those not protected will have a greater chance of developing the disease". However, in claiming a prophylactic method, the specification must show that the claimed method can prevent the disease being treated. The specification herein fails to show the administration of NH2-olpadronate is capable of maintaining a bone structure that is free of any osteopathies. As such, the rejection under section 112, first paragraph is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-33, 35-37, 54, and 58-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants recite, "said method comprising administering to a patient without an osteopathy." There are no clear cut limitations on when a patient has an osteopathy versus when the patient doesn't. Many of the bone related diseases are progressive diseases, and most can only be diagnosed after they have multiple symptoms. Thus, how would a skilled artisan know when a patient has an osteopathy, versus when the patient is without an osteopathy? How is it determined? It is not clear which ones do applicant point to as representative of "a patient without an osteopathy"? Does a patient without an osteopathy have NO clinical signs? OR, do they have some clinical signs, but are still considered "healthy" (i.e. no outward appearance of osteopathy). As such, it is not clear how one would identify a patient without osteopathy and one of skill in the art would not be able to ascertain the metes and merits of the claims herein.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants argue that the web pages in exhibits A-C are examples of how to diagnose osteopathy. However, the exhibits are directed to

diagnosing osteoporosis, not diagnosing "a patient with an osteopathy". Applicants' seem to equate osteoporosis with osteopathy. These two terms vary in scope and osteoporosis is a subset of osteopathy. Since the claims herein are directed to a patient without an osteopathy, one of skill in the art would need to diagnose all osteopathies, not just a subset of it. The rejection under section 112, second paragraph is deemed proper and is adhered to.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims recite the phrase, "post-treatment of osteopathies". It is not clear whether the claim require a patient to be free of osteopathies as a result of treatment of osteopathies or whether after some treatment for osteopathies is given. As such, one of skill in the art would not be able ascertain the metes and bounds of the claim herein.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants argue that, "there is no basis in the claim itself to believe that the patient is required to be free of osteopathy", and that one of ordinary skill in the art would understand the meaning of the word "post treatment." Applicants further note that those skilled in the art understand the term "post-treatment" to mean the time when the prescribed basic treatment ends. However, the term can interpreted to include anyone who has received

any form of treatment of osteopathies at any time during their life span. Since the term osteopathy itself includes a large number of diverse diseases such as arthritis, fracture, back pain etc. it is not clear what type of treatment is considered to be included in the instant claims. Since no specific osteopathy treatment was contemplated for post-treatment in the specification one of skill in the art would not be able to ascertain the scope of the claims herein. As such the rejection under section 112, second paragraph is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 60 and 63-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Beek et. al. (WO 97/02827; Of record).

Van Beek et. al. discloses the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3). Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone. (Page 4, Paragraph 2; Claims 5-10, Page 15). Beek et. al. further

discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is devoid of any antiresorptive activity. (Page 5, Paragraph 3, lines 1-5). 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is disclosed as useful in the treatment of diseases in which antresorptive action is unwanted. . (Page 5, Paragraph 3, lines 5-10). Osteoporosis, arthritis and periodontal diseases are considered bone disorders. Example 4 and Figure 1 shows binding of bone mineral by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as well as olpadronate at various concnetrations. Example 5 and Figure 2 shows inhibition of calcium incorporation by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and similar compounds. Half maximal inhibition for 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid was disclosed as $2x10^{-7}$M. (Page 11, last paragraph). Van Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid inhibited crystal growth with half maximal concentrations of $3x10^{-6}$ M. (Example 6, page 12). These concentrations are considered to fall in the claimed range of a "bone health promoting effective amount". Furthermore, the effects such as "increase in osteocalcin synthesis in the osteoblast cells" and "cause an increase in cytosolic calcium concentration of the osteoblast cells" are considered functional descriptions of inherent properties derived from the administration of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants argue that, van Beek only teaches "concentrations" of NH2-olpadronate, but not "amounts". Applicant points to claim 61 for the limitation of ranges 0.1-1000 and 0.02-200mg. However, claim 61 was not rejected under section 102(b) over van Beek et. al. Applicants further argue that "the concentrations of Nh2-olpadronate disclosed in Van Beek do not disclose an effective amount of NH2-olpadronate". Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions to determine whether the concentration is in fact an effective amount, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). The rejection under section 102(b) is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-45 and 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Beek et. al. (WO 97/02827; Of record) in view of Brumsen et. al. (Reviews in Molecular Medicine, 76(4), 1997, pp266-283; Of Record).

Van Beek et. al. discloses the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3). Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone. (Page 4, Paragraph 2; Claims 5-10, Page 15). Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is devoid of any antiresorptive activity. (Page 5, Paragraph 3, lines 1-5). 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is disclosed as useful in the treatment of diseases in which antresorptive action is unwanted. . (Page 5, Paragraph 3, lines 5-10). Since the treatment of all forms of osteoporosis and arthritis and periodontal diseases is required "for maintaining a healthy bone structure", said treatment is considered encompassed by the "method for maintaining a healthy bone structure". Example 4 and Figure 1 shows binding of bone mineral by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as well as olpadronate at various concnetrations. Example 5 and Figure 2 shows inhibition of calcium incorporation by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and similar compounds. Half maximal inhibition for 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid was disclosed as $2x10^{-7}M$. (Page 11, last

paragraph). Van Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid inhibited crystal growth with half maximal concentrations of $3x10^{-6}$ M. (Example 6, page 12). These concentrations are considered to fall in the claimed range of a "bone health promoting effective amount". Furthermore, Beek et. al. discloses that in comparison with olpadronate, 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid has similar binding activity (Figure 1) while without the undesired antiresorptive activity. (Figure 7; Page 5, Paragraph 3, lines 1-5).

Beek et. al. does not expressly disclose the use of NH2-OPD for administration to healthy patients or patients without osteopathies to human being at or above the age of 40 years or to a child or for patients who have undergone corticosteroid treatment or for combating bone disease in a child or any particular dosage range.

Brumsen et. al. discloses the use of 1-hydroxy-3-(N,N-dimethylamino)-propylidene-1,1-bisophosphonate (olpadronate), a molecule with strong structural similarity to 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. Note that the only difference between the two compounds is the substitution of the hydroxyl group for the amine group at 1-position. Brumsen et. al discloses that long term olpadronate administration to children severe osteoporosis was devoid of any adverse effect on the growing skeleton. (Web printout; Page 20, Paragraph 2). Brumsen et. al. discloses the use of bisphosphonates for patients who underwent glucocorticoid treatment. (Web printout; Page 21, Paragraph 1). Brumsen et. al further discloses that bisphosphonates are well known for

treatment for patients with postmenopausal osteoporosis, a condition generally affecting those above 40 years age.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to treat children in place of olpadronate because Brumsen et. al. discloses olpadronate for the treatment of children and Beek et. al. discloses 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to have superior antiresoprtive activity (i.e. lacking the undesired antiresorptive activity) in direct comparison with olpadronate. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat healthy patients, and patients without osteopathies with 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid because it is devoid of any unwanted antiresorptive activity and beneficial effects. Furthermore, Beek's disclosed use for diagnostic purposes is expected to include healthy individuals as well as individuals without osteopathies. Furthermore, it is considered to be within the basic skills of one of ordinary skill in the art to select appropriate dosage levels for one of various diseases considered as bone disorders. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). All the claimed steps herein are known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the

art at the time of the invention. Furthermore, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp and results of such efforts is considered common sense, rather than a product of innovation.

One of ordinary skill in the art would have reasonably expected that the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as claimed herein would be successful because Beek et.al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects.

Thus the invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants argue that rebuttal evidence of unexpected properties of NH2-olpadronate must be considered. Applicant submit that NH2-olpadronate has unexpectedly no antiresorptive activity. However, this effect cannot be considered unexpected since it was recognized in the prior art as discussed above. Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex Parte Gelles,* 22 USPQ2d 1318, 1319 (Bd. Pat. App & Inter. 1992). Since Van Beek itself has recognized the anti-resroptive of NH2-olpadronate in the prior art and disclosed its use for treatments of various osteopathies, the results themselves cannot be

considered unexpected. As such, the rejection under section 103 is still deemed proper and is adhered to.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Roy P. Issac
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623